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Genetic Heterogeneity of Familial Dyslipidemia: Real-World Evidence from a Large Colombian Cohort

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Abstract

Background: Familial dyslipidemia (FD) comprises a heterogeneous group of genetic disorders of lipoprotein metabolism associated with premature cardiovascular disease, with familial hypercholesterolemia being the most extensively characterized. Despite their clinical relevance, the genetic architecture of FD remains poorly described in Latin American populations, limiting risk stratification and genetic counseling in the region.

Methods: A retrospective and pragmatic cohort study (September 2020–July 2025) was conducted on 860 Colombian patients referred for whole-exome sequencing (WES) with a clinical suspicion of FD. Patients were recruited from a national reference laboratory serving the EPS Sanitas healthcare network. While all patients underwent WES, analysis strategies included 616 targeted exomes (filtered through a gene panel); additionally, 198 singleton exomes, 42 trio exomes, and 4 duo exomes. Variants were classified according to the American College of Medical Genetics and Genomics (ACMG) criteria.

Results: The overall positivity rate was 14.88% (128/860). This rate varied according to age and clinical phenotype and was highest in young adults (21.83%) and in patients with hypercholesterolemia (17.39%). The *LDLR* gene accounted for the majority of the positive findings (94 variants), followed to a lesser extent by *APOB* and *LPL*; fourteen large deletions (CNVs) in *LDLR* completed the molecular landscape. The geographic distribution was heterogeneous: the highest positivity rates were recorded in Magdalena (42.86%) and Sucre (37.50%), while the lowest were recorded in Bogotá (~11%) and Antioquia (<10%), with specific variants clustering by region (e.g., *LDLR* c.11G>A in Cesar and Bogotá; c.1246C>T in Tolima–Caldas–Valle del Cauca). Notable findings included the first Colombian case of the Lebanese allele (*LDLR* c.2043C>A), a novel *LDLR* variant (c.1955T>G) segregating in two sisters, and 0.58% of cases presenting with homozygous dyslipidemia. Additionally, our results demonstrated that a larger panel size does not increase the positivity rate of the genetic test; specifically, 25 of the 37 genes (67.6%) yielded no diagnostic findings of the genetic test.

Conclusions: This study represents the most extensive genomic characterization of FD in a Colombian cohort to date to our knowledge. The findings reveal marked genetic heterogeneity without a single dominant founder allele, reflecting the ancestral admixture of the Colombian population. These results support the need for more selective, clinically impact-driven criteria when genetic testing is requested. Furthermore, they underscore the urgent need for national cascade screening programs to make precision medicine for FD accessible throughout the Colombian territory.

Introduction

Lipid metabolism disorders constitute a fundamental axis of epidemiological surveillance and research, as they are key determinants of chronic metabolic health. This importance is largely driven by their established role in the onset of premature cardiovascular disease[1]. A significant subgroup of these conditions, known as familial dyslipidemias (FD), stems from genetic alterations that disrupt the homeostasis of various lipoproteins[2]. The most prominent representative of this group is familial hypercholesterolemia (FH), which is associated primarily with impaired function of the low-density lipoprotein (LDL) receptor. However, this group of diseases also encompasses a broader spectrum of inherited disorders affecting triglyceride-rich lipoproteins and other lipid fractions, such as hypertriglyceridemia, mixed dyslipidemias, hyperlipoproteinemia, familial hypobetalipoproteinemia, and chylomicronemia.

Within the Colombian healthcare context, a patient's initial therapeutic pathway may not change immediately following a molecular diagnosis. Nevertheless, the identification of a genetic etiology fundamentally shifts the clinical paradigm by improving prognostic accuracy and guiding long-term treatment intensity, as well as, cascade screening of first-degree relatives to evaluate familial inheritance of the metabolic disorder. Consequently, ensuring access to genomic studies is essential for the precise stratification of these patients. Despite its clinical value, international evidence has revealed significant barriers to accessing genetic testing and implementing effective cascade screening, which remains a challenge for familial prevention[3], [4].

This study presents the results obtained through next-generation sequencing (NGS) in a large, real-world cohort of 860 patients with suspected FD. Furthermore, this study provides data on the clinical behavior of familial dyslipidemias in Colombia—information that is currently scarce in the literature and lacks representation in descriptions of large Latin American cohorts.

Materials and methods

Study design and participants

Between September 2020 and July 2025, a retrospective cohort study was conducted at the Genomics Unit of the Keralty Laboratory (Bogotá, Colombia). This institution processes genetic testing samples sourced from a network of hospitals and laboratories located across different regions of Colombia. A total of 14,153 patients were selected from a comprehensive clinical genomic database. This cohort comprised individuals who had previously undergone whole-exome sequencing (WES) as part of the diagnostic workup for various suspected genetic disorders. Among these, 860 (616 targeted exomes, 198 singleton exomes, 42 trio exomes, and 4 duo exomes) patients were admitted with a clinical suspicion of familial dyslipidemia (FD) and were referred by various specialists from major cities and departments across Colombia. A total of 852 patients were born in a Colombian department, whereas 8 were foreign nationals.

This study employed a pragmatic design, as the investigators did not preselect the included patients. Prior to admission to the Genomics Unit, all patients were evaluated by their respective attending physicians. During this evaluation, the physicians reviewed the patients' personal and family medical histories

regarding premature coronary heart disease, cardiovascular events, and severe early-onset dyslipidemia. At the institutional level, exome sequencing was indicated for patients with suspected FD who met at least one of the following criteria:

Extreme lipid alterations: Significantly elevated LDL cholesterol (LDL-C ≥ 190 mg/dL in adults; LDL-C ≥ 160 mg/dL in children up to 5 years of age; or LDL-C ≥ 130 mg/dL in the presence of a family history of premature atherosclerotic cardiovascular disease or a history in one of the parents); extremely low HDL cholesterol (HDL-C); triglycerides > 200 mg/dL; or altered levels of Lipoprotein(a) [Lp(a)] and Apolipoprotein B (ApoB).

Complex or mixed phenotypes: Mixed dyslipidemias, refractoriness to conventional treatment, or a high score on the Dutch Lipid Clinic Network (DLCN) criteria.

Clinical manifestations: Presence of xanthomas, xanthelasmas, or premature corneal arcus; recurrent or cryptogenic pancreatitis; hepatic steatosis, hepatomegaly, or unexplained elevated transaminases.

Age and family history: Onset in childhood or young adulthood, or a family history of dyslipidemia or premature cardiovascular disease in a first-degree relative. Additionally, there needs to be a previously identified pathogenic (P) or likely pathogenic (LP) variant in a first-degree relative.

Data sources and covariates

Data were obtained primarily from electronic health records (EHR) and the laboratory information management system (LIMS) to collect comprehensive demographic and clinical information. The extracted variables included age, patient identification number, city of origin, and sex.

Participants were classified into four age groups according to the guidelines of the World Health Organization (WHO) and the Colombian Ministry of Health[5]: pediatric (0-17 years), young adults (18-40 years), adults (41-60 years), and older adults (≥61 years).

Regarding to biochemical data, the analysis focused on the mean baseline values of the lipid profile components across the entire cohort, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG), all measured in mg/dL.

Sample processing

Genomic DNA (gDNA) was extracted and quantified to ensure sample homogeneity. Library preparation and sequencing were performed using the following systems: Illumina DNA Prep with Enrichment (Illumina NovaSeq 6000), MGI V5 (DNBSEQ-G400, MGI Tech Co.), and Twist Comprehensive Exome v1 (Illumina NovaSeq 6000). The workflow included tagmentation, unique dual index (UDI) ligation, and initial amplification, followed by pooled hybridization enrichment using biotinylated probes targeting exonic regions. The final libraries were validated through fragment analysis (~330 bp) and fluorometric quantification (>3 ng/µL). Sequencing quality control parameters consistently achieved a target base coverage of ≥98% at a minimum depth of 20X.

Bioinformatic analysis

Primary data processing and mapping to the GRCh37/GRCh38 reference genomes were performed via the Sophia DDM and VarSome Clinical platforms, employing the BWA algorithm. Variant calling was executed with GATK, followed by a multistage annotation process using the A-GPS®, I-GPS®, and D-GPS® pipelines. A targeted panel of 37 FD-associated genes derived from multiple commercial panels was analyzed:

Cholesterol metabolism disorders genes: (LDL, HDL): *ABCA1, ABCG5, ABCG8, APOA1, CETP, LCAT, LDLR, LDLRAP1, LIPA, LIPG, LPA, LRP6, MYLIP, NPC1L1, PCSK9,* and *SCARB1*.

Triglyceride metabolism disorder genes: *ANGPTL3, APOA5, CELA2A, CREB3L3, EPHX2, GHR, GPD1, GPIHBP1, LMF1, LPL, PNPLA2, PPARG, PPP1R17,* and *SAR1B*.

General lipoprotein metabolism genes *APOB, APOC2, APOC3, APOE, LIPC,* and *MTTP*.

Fatty acid metabolism gene included: *ABCD1*.

Variants were classified according to the ACMG criteria[6] and categorized as pathogenic (P), likely pathogenic (LP), or variants of uncertain significance (VUS). Synonymous or deep intronic variants without a predicted impact on splicing were excluded unless they had been previously reported as pathogenic. Copy number variation (CNV) analysis was limited to events affecting one or more exons and MLPA was recommended for confirmation of findings in every case Finally, the genomic findings were correlated with the clinical phenotypes and lipid profiles obtained from the EHR.

Data Sharing Restrictions

Due to the sensitive nature of clinical data and strict institutional policies regarding patient privacy and confidentiality, the raw clinical dataset cannot be deposited in an unrestricted public repository. Unrestricted public sharing of individual clinical records was not authorized under the institutional review board approval or participant consent. To comply with ethical standards while supporting open science, all necessary de-identified and aggregated data required to evaluate the conclusions are provided within the supplementary files.

Statistical analysis

Statistical analysis was performed via analysis of variance (ANOVA). The results were described via descriptive statistics, according to the nature of the variables. Categorical variables are expressed as absolute frequencies and percentages, whereas continuous variables are expressed as the means.

Ethics approval and consent to participate

Written informed consent (LAB-TM-FO-010) was obtained from all adult participants prior to inclusion. For participants under 16 years of age, written informed consent was obtained from their parents or legal guardians, along with the assent of the minors where applicable. As part of the sampling procedure, participants (or their legal representatives) agreed to the anonymous use of their data and results for research

and publication purposes. Furthermore, the research protocol was reviewed and approved by the Research Ethics Committee of the Fundación Universitaria Sanitas (protocol number CEIFUS 187-26), in strict accordance with the ethical standards of the Declaration of Helsinki and its later amendments.

Results

Cohort description

A total of 860 patients were referred for genomic evaluation on the basis of a clinical phenotype compatible with dyslipidemia, constituting the primary analysis cohort. The sequencing strategies employed included 616 targeted exomes, 198 singleton exomes, 42 trio exomes, and 4 duo exomes. The mean baseline lipid profile values for the 860 patients were as follows: TC, 254 mg/dL; HDL-C, 51 mg/dL; LDL-C, 164 mg/dL; and TG, 220 mg/dL.

The age of the cohort ranged from 1 to 79 years (mean = 41; SD = 19.95). Within this group, 514 patients were female (59.76%), with a mean age of 43 years, and 346 were male (40.23%), with a mean age of 39 years.

The initial diagnoses documented in the EHRs were as follows: 598 patients (69.53%) had hypercholesterolemia, 130 (15.12%) presented with mixed dyslipidemia (hypercholesterolemia and hypertriglyceridemia), 66 (7.67%) had isolated hypertriglyceridemia, 8 (0.93%) had hyperlipoproteinemia (a), 2 (0.23%) had chylomicronemia, 1 (0.12%) had familial hypobetalipoproteinemia, 48 (5.59%) had other unspecified dyslipidemias, and 7 (0.80%) were referred due to family history. Among the 860 analyzed patients, 10 (1.16%) presented with xanthomas, 5 (0.58%) with xanthelasmas, and 17 (1.97%) with a corneal arcus; additionally, 13 (1.50%) reported episodes of recurrent pancreatitis. The remaining 815 patients (94.76%) did not report any physical findings of lipid deposits or a history of pancreatitis in their medical records. This emphasizes that traditional criteria may be insufficient for suspecting genetically caused hyperlipidemia in our population.

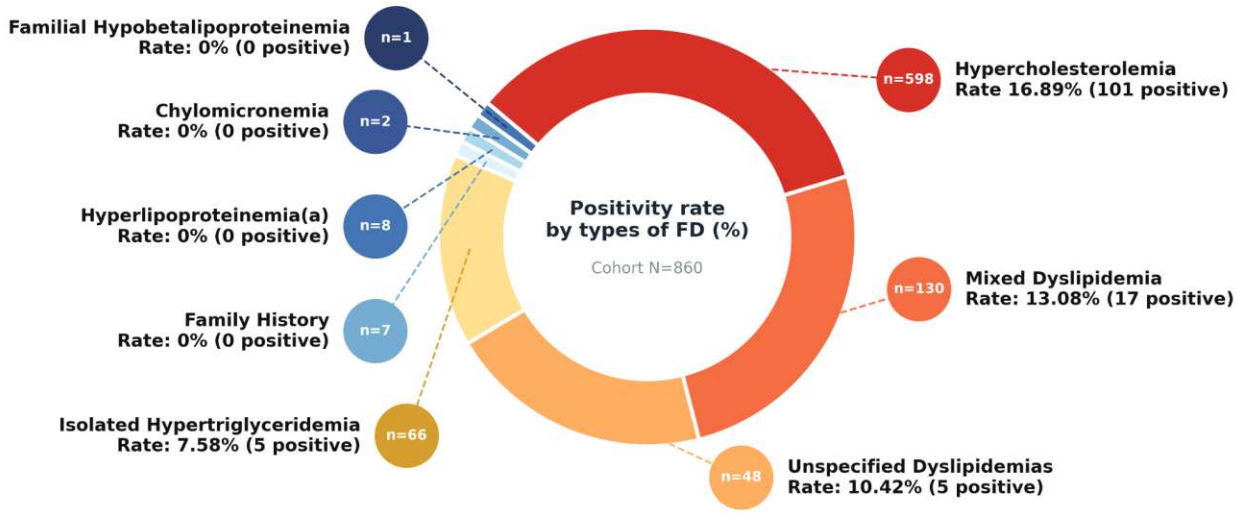


Figure 1. Positivity rate by type of familial dyslipidemia.

In the cohort of patients with clinical suspicion of FD, 128 positive cases (14.88%) were identified (Figure 1), defined as those harboring pathogenic (P) and/or likely pathogenic (LP) variants, including single nucleotide variants (SNVs) and/or copy number variations (CNVs). Among these patients, 76 (59.4%) were female, and 52 (40.6%) were male. Furthermore, variants of uncertain significance (VUS) were identified in 52 patients (6.04%), whereas 668 patients (77.67%) had a negative result, defined as the absence of clinically relevant variants across the 37 evaluated genes. Finally, 12 patients were symptomatic carriers (1.40%).

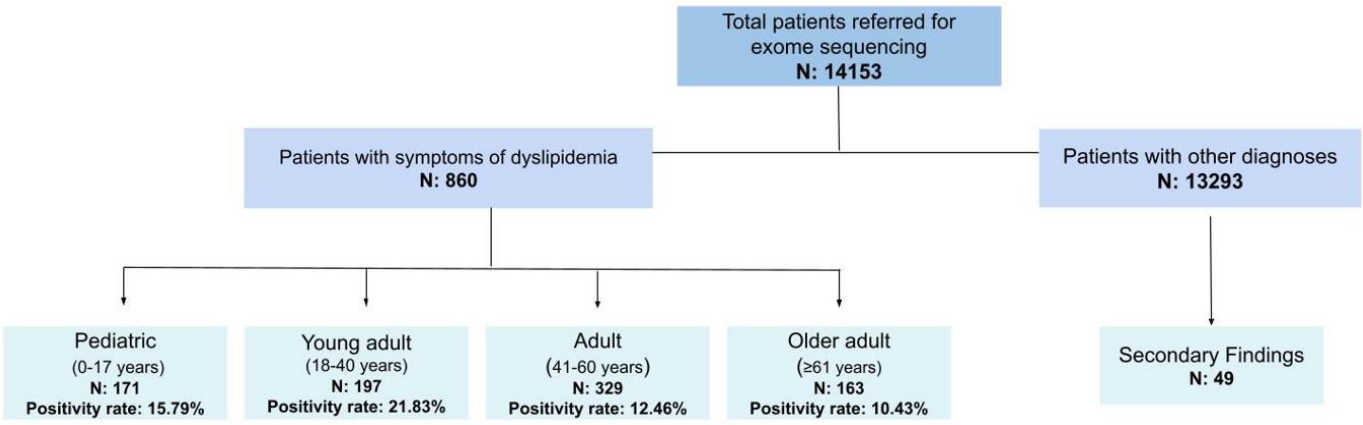


Figure 2. Study flowchart of the patients and positivity rate of exome sequencing for hereditary dyslipidemias.

The overall positivity rate was 14.88%, with the highest positivity rate observed among young adults (21.83%) (Figure 2). Among the positive cases, missense variants were the most common (Figure 3), followed by nonsense and intronic variants, whereas frameshift, indel, synonymous and splice site variants occurred less frequently. Furthermore, 14 large LDLR copy-number deletions were identified, spanning 2.2–7.2 kb and disrupting critical exonic regions; these variants were associated with more severe phenotypic expression.

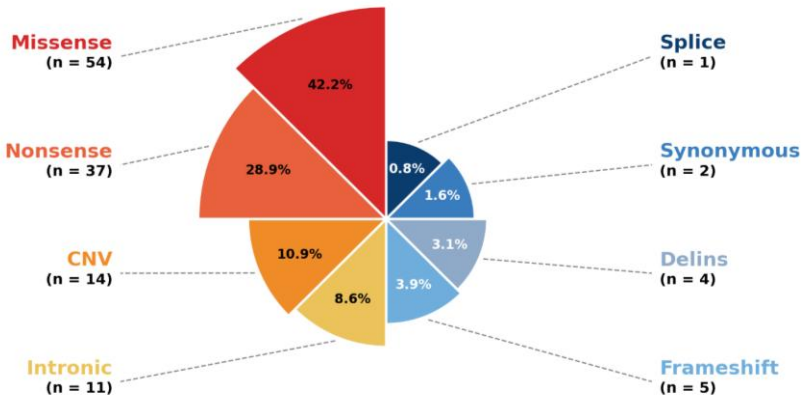


Figure 3. Number of findings identified by type of associated variants (P/PP)

The mean baseline lipid profiles of patients harboring P/LP variants in various FD-associated genes, stratified by the type of genetic variant, are summarized in Table 1. A total of 111 out of the 128 genetically positive patients in our cohort had available lipid profiles (n=111). Statistical analysis was performed via analysis of variance (ANOVA) to determine whether there were significant differences in TC, HDL-C, LDL-C, and TG levels depending on the type of mutation present in each patient. As shown in Table 1, the comparison of lipid profiles revealed statistically significant differences in LDL-C ($p = 0.03$). In contrast, the mutations did not significantly affect general fat metabolism (TG, $p = 0.13$) or high-density lipoprotein (HDL-C, $p = 0.78$) levels. Instead, their impact is concentrated exclusively on the LDL cholesterol pathway, which is more moderately reflected by the trend observed in total cholesterol (TC, $p = 0.07$).

	Protein-truncating n=39	**Missense n=45**	**Others n=27**	**p value (< 0.05)**
TC [mg/dL]	312± 107,5	272± 92,1	271± 104,5	0.07
HDL-C [mg/dL]	46± 13,5	48± 18.2	65± 91	0.78
LDL-C [mg/dL]	233± 102,6	182± 92.4	193± 103	0.03
TG [mg/dL]	148± 104,5	210± 234,8	166± 205,2	0.13

Table 1. Comparative summary of patient lipid profile values according to variant type. HDLC:highdensity lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: total triglycerides. Protein truncating: nonsense, frameshift and splicing variants. Others: delins, inframes, intronic, synonymous variants and CNVs.

Among the 37 genes evaluated, pathogenic and/or likely pathogenic variants were identified in only 11 of them (*LDLR, CELA2A, CREB3L3, LIPA, ABCG8, APOB, ABCG5, LPL, ABCD1, APOE*, and *APOA5*). Consequently, 26 of the 37 genes (70.3%) did not yield any diagnosis.The *LDLR* gene was the most commonly mutated gene across all age groups, harboring 108 variants, and reached its highest prevalence among young adults (37.5%). Other recurrently mutated genes included *APOB* (4.68%), identified mainly in adults and older adults, and *LPL* (3.12%), found predominantly in the adult population (Figure 4).

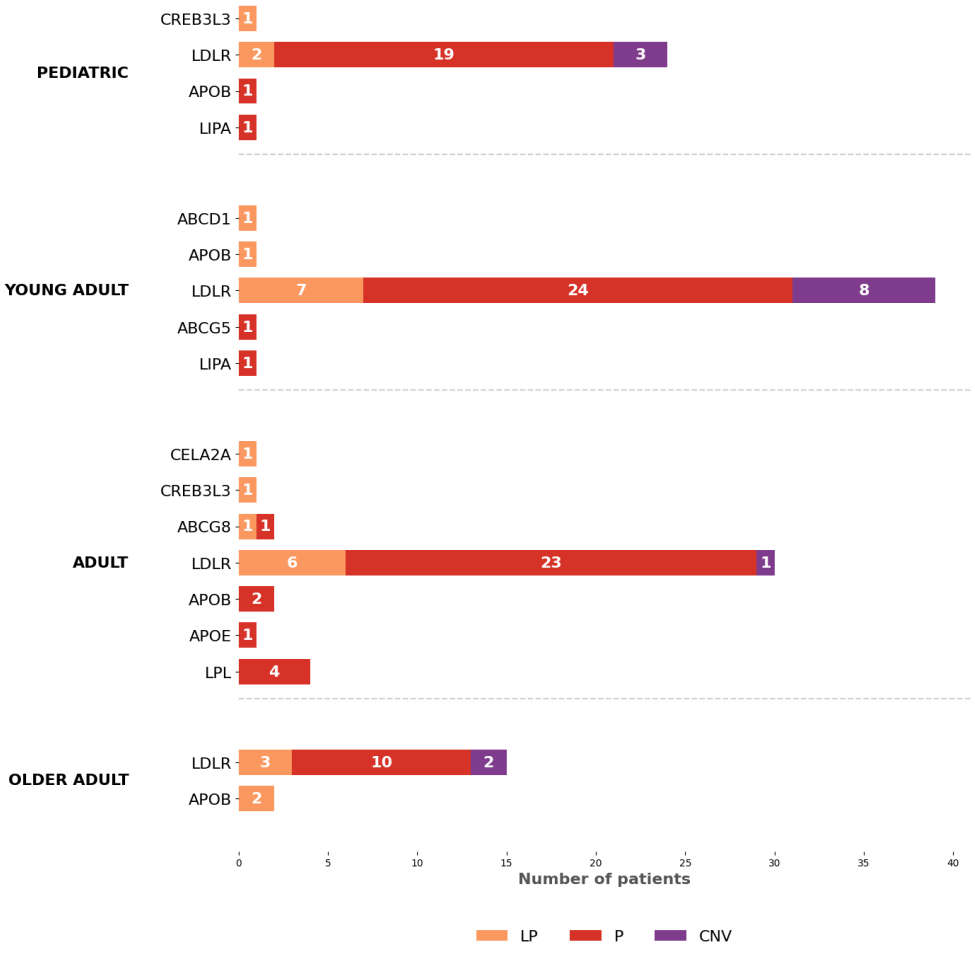


Figure 4. Distribution of total findings (SNVs) by age group and variant classification. P: pathogenic; LP: likely pathogenic.

As shown in Figure 4, among the young adult and adult populations, three homozygous variants (encompassing both pathogenic and likely pathogenic classifications) were observed in the *LDLR*, *ABCG5*,

and *ABCG8* genes, along with one hemizygous variant in the *ABCD1* gene. On average, these patients presented with significantly elevated TC (>300 mg/dL), LDL-C (>200 mg/dL), and TG levels ranging from 100 to 300 mg/dL. Furthermore, they had a history of high premature cardiovascular risk, with some individuals in the adult population already exhibiting coronary artery disease.

The study group also included symptomatic carriers. These individuals were heterozygous carriers of variants in genes associated with recessive phenotypes, including carriers of the *LIPA*: c.894G>A (p.Gln298=) variant, a synonymous alteration with a well-established pathogenic splice-site defect, and 11 heterozygous pathogenic variants in the *ABCG5* and *ABCG8* genes. These patients presented relatively high levels of cholesterol and triglycerides.

Geographical distribution of familial dyslipidemias in Colombia

Geographical distribution was determined on the basis of the patients' places of origin, with cases concentrated primarily in the Andean and Caribbean regions (Figure 5). The highest positivity rates were observed in Magdalena (42.86%) and Sucre (37.50%), followed by Cesar (28.21%), Valle del Cauca (26.39%), Quindío (27.27%), and Córdoba (25.00%). Conversely, the lowest rates were recorded in Bogotá D.C. (10.85%), Meta (10.00%), Antioquia (8.33%), and Boyacá (8.16%).

In Bogotá, a high frequency of variants in genes associated with familial dyslipidemia was identified, particularly in *LDLR, APOB, LPL, CREB3L3, LIPA*, and *ABCG5*. Genomic analysis revealed distinctive regional patterns: Valle del Cauca presented the highest frequency of 2.2 kb deletions (n=11) at the 19p13.2 locus affecting the *LDLR* gene. In Santander, the *LDLR* c.682G>A (p.Glu228Lys) variant was the most representative (n=7), whereas the pathogenic null variant *LDLR* c.11G>A (p.Trp4*) predominated in Cesar and Bogotá (n=7 and n=8, respectively). Notably, the *LDLR* c.1246C>T (p.Arg416Trp) variant showed geographical clustering in Tolima, Caldas, and Valle del Cauca.

Regardless of their geographical origin, all individuals positive for *APOB* exclusively carried the c.10580G>A (p.Arg3527Gln) variant. Supplementary Table 1 provides a detailed description of the P/LP variants and geographical origins of the patients.

Finally, an older adult female patient from the Atlantic region (Barranquilla) with a strong family history of hypercholesterolemia was identified as a carrier of the 'Lebanese allele'[7] (*LDLR* c.2043C>A; p.Cys681*). This variant is a nonsense mutation originally described by Lehrman et al. as a characteristic founder effect of familial hypercholesterolemia in Middle Eastern populations. This mutation generates a truncated and nonfunctional receptor, which translates into a clinical phenotype of severe hypercholesterolemia.

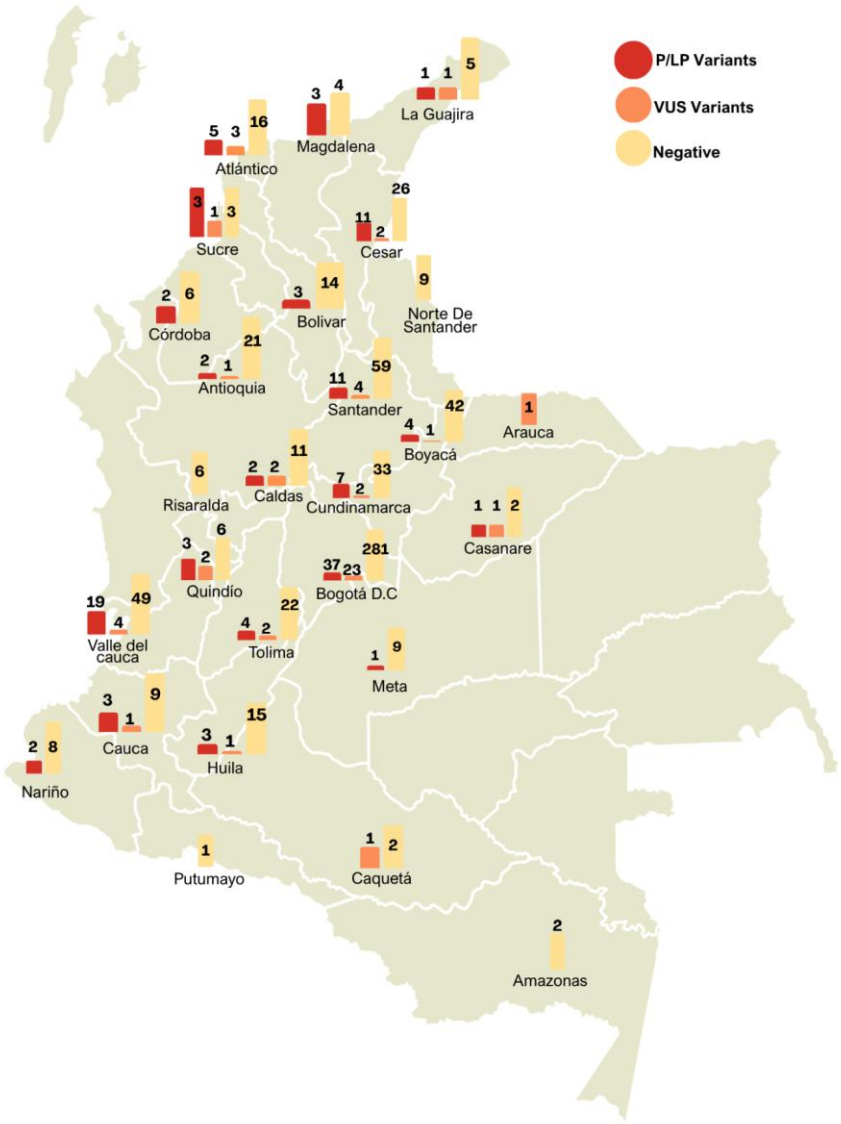


Figure 5. Colombian distribution of P/LP variants, VUS, and negative results in patients with suspected FD. P: pathogenic; LP: likely pathogenic; VUS: variant of uncertain significance.

Genotypic characterization

Table 2 details the identified variants, categorizing them into simple homozygous, hemizygous, compound heterozygous, double heterozygous, simple heterozygous, and CNVs. The co-occurrence of variants in dyslipidemia-related genes was identified in three patients, although only one involved two P/LP variants. This case corresponded to a 9-year-old girl whose trio exome analysis revealed two paternally inherited frameshift variants: a pathogenic variant in *LDLR* (c.2068del; p.His690Thrfs*19) and a likely pathogenic variant in APOA5 (c.124del; p.Glu42Serfs*15). Clinically, the patient presented with severe hypercholesterolemia (TC: 406 mg/dL; LDL-C: 333.94 mg/dL; HDL-C: 51 mg/dL; TG: 109 mg/dL) and required ezetimibe due to an inadequate response to atorvastatin. Her family history was significant: an 18-year-old sister with hypercholesterolemia and a father with a history of myocardial infarction at age 42, currently receiving treatment with rosuvastatin/ezetimibe (40/10 mg).

Family segregation analysis of 42 trios confirmed five positive cases and two VUS, all of which were inherited from parents with a clinical history of dyslipidemia.

Characteristic	Gene	Mutation (DNA)	Mutation (Protein)	Type of variant	ACMG	n
Simple homozygotes	*LDLR*	c.1694G>A	p.Gly565Asp	Missense	LP	1
	ABCG8	c.1488+2T>G	-	Splice	LP	1
		c.647_657dup	p.Arg220Valfs*37	Frameshift	P	1
	ABCG5	c.1890del	p.Phe630Leufs*8	Frameshift	P	1
Hemizygotes	*ABCD1*	c.566G>A	p. Arg189Gln	Missense	LP	1
Compound heterozygotes	*LDLR*	c.185C>T/c.1246C>T	p.Thr62Met/p.Arg416Trp	MS/MS	VUS/LP	1
		c.502G>A/c.682G>A	p.Asp168Asn/p.Glu228Lys	MS/MS	P/P	1
		c.116G>A/c.185C>T	p.Cys39Tyr/p.Thr62Met	MS/MS	LP/VUS	1
	LIPA	c.386A>G/c.894G>A	p.His129Arg/p.Gln298=	MS/SY	P/LP	1
		c.739G>A/c.894G>A	p.Val247Ile/p.Gln298=	MS/SY	VUS/P	1
Double heterozygotes	*LDLR & APOB*	c.-135C>G/c.4162C>T	-/p.Arg1388Cys	PR/MS	P/VUS	1
	LDLR & LPL	c.1246C>T/c.629A>G	p.Arg416Trp/p.His210Arg	MS/MS	P/VUS	1
	LDLR & APOA5	c.2068del/c.124del	p.His690Thrfs*19/ p.Glu42Serfs*15	FS/FS	P/LP	1
Simple heterozygotes	*LDLR*	c.11G>A	p.Trp4*	Nonsense	P	29
		c.-135C>G	-	Promoter	P	11
		c.1246C>T	p.Arg416Trp	Missense	P	7
		c.682G>A	p.Glu228Lys	Missense	P	8
		c.1187-1_1187delinsTA	-	Delins	P	4
		c.502G>A	p.Asp168Asn	Missense	P	3
		c.1216C>T	p. Arg406Trp	Missense	P	2
		c.1694G>A	p.Gly565Asp	Missense	LP	2
		c.1955T>G	p.Met652Arg	Missense	LP	2
		c.2230C>T	p.Arg744*	Nonsense	P	2
		c.482T>A	p.Ile161Asn	Missense	LP	2
		c.1048C>T	p.Arg350*	Nonsense	P	1
		c.1072T>C	p.Cys358Arg	Missense	LP	1
		c.1118G>A	p.Gly373Asp	Missense	LP	1
		c.1216C>A	p.Arg406=	Synonymous	LP	1
		c.12G>A	p.Trp4*	Nonsense	P	1
		c.1335C>A	p. Asp445Glu	Missense	LP	1
		c.1361C>A	p.Thr454Asn	Missense	LP	1
		c.1382del	p.Gly461Alafs*46	Frameshift	P	1
		c.1688C>T	p.Pro563Leu	Missense	LP	1
		c.1878del	p.Ala627Profs*38	Frameshift	P	1
		c.2043C>A	p.Cys681*	Nonsense	P	1
		c.274C>T	p.Gln92*	Nonsense	P	1
		c.626G>A	p.Cys209Tyr	Missense	LP	1
		c.760C>G	p.Gln254Glu	Missense	LP	1
		c.862G>A	p.Glu288Lys	Missense	P	1
		c.986G>T	p.Cys329Phe	Missense	LP	1
	APOB	c.10580G>A	p.Arg3527Gln	Missense	P	6
	CELA2A	c.253C>A	p.Leu85Met	Missense	LP	1
	CREB3L3	c.603C>A	p.Tyr201*	Nonsense	LP	2
	LPL	c.644G>A	p.Gly215Glu	Missense	P	4
Large deletions (CNVs)	*LDLR*	-	-	CNV	LP	14

Table 2. Genetic variant frequencies and their correlation with peak median TC, HDL-C, LDL-C, and TG levels per genotype. Abbreviations: TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglycerides; FS: frameshift; MS: missense; PR: promoter; IN: intronic; SY: synonymous; n: total number of patients with the characteristic.

Finally, within our cohort, we identified the novel *LDLR* c.1955T>G (p.Met652Arg) variant in a heterozygous state in two sisters, aged 37 and 40 years, both with a clinical diagnosis of severe dyslipidemia. The first sister presented with mean TC levels of 380 mg/dL, an HDL-C of 210 mg/dL, and an LDL-C of 256 mg/dL; the second sister presented a mean TC of 307.9 mg/dL, an HDL-C of 64 mg/dL, and an LDL-C of 225 mg/dL. Additionally, both patients reported an extensive family history of severe hypercholesterolemia. The patients achieved a score of 12 on the Dutch Lipid Clinic Network criteria.

Secondary findings in the cohort

As illustrated in Figure 2, in addition to the 860 patients with a clinical suspicion of hereditary dyslipidemia, relevant genetic findings were identified in 49 individuals who did not exhibit a compatible clinical phenotype at the time of the study, among the total study population of over 14.000 patients. In these subjects, 28 unique pathogenic or likely pathogenic (P/LP) variants were detected within the 84 actionable genes recommended for reporting. These findings were categorized as secondary findings according to the ACMG SF v3.3 recommendations when identified in the *LDLR*, *APOB*, or *PCSK9* genes. The *LDLR* gene was the most frequently affected gene, with 37 patients harboring P/LP variants, followed by *APOB* in 9 patients and *PCSK9* in 3 patients.

Discussion

To the best of our knowledge, this study describes the largest cohort of familial dyslipidemias in Colombia to date. Additionally, this study provides the first data on the geographical distribution of FD-associated variants across different Colombian regions.

Positivity rate and age-related dynamics

The overall positivity rate in this study was 14.88%, which aligns with global benchmarks[8] reporting a rate of approximately 15%. However, our findings suggest that the positivity rate is significantly influenced by patient age, phenotype severity, and referral criteria. We observed a marked decrease in positivity rates among patients older than 61 years, a phenomenon that could be attributed to survival bias and early detection; patients with severe familial forms are typically identified and treated by their fifth decade of life owing to greater clinical expressivity[9]. Furthermore, age-related comorbidities frequently lead to secondary dyslipidemia, potentially confounding the genetic diagnosis in older age groups[10].

In contrast, the 41–60 years age group accounted for the highest testing volume, likely reflecting increased cardiovascular screening during middle age. The intermediate positivity rate in this group can be attributed to etiological heterogeneity, where monogenic variants coexist with an increasing burden of environmental factors[11]. Conversely, young adults presented the highest positivity rate, which is consistent with a greater probability of early-onset monogenic dyslipidemia and a lower number of acquired confounding factors[12].

In our pediatric cohort, the positivity rate (15.79%) was significantly lower than that reported in international studies. While countries with established screening programs, such as the Netherlands, achieve detection rates of 95% for gene panels, including *LDLR*, *APOB*, or *PCSK9*, and countries such as Slovenia and Italy range between 50% and 57%[13], our results show a significantly lower yield. This discrepancy may be linked to the high prevalence of childhood obesity in Colombia (17.53%) [14] and the lack of a national

pediatric screening program. Finally, the high rate of negative results across the entire cohort suggests a significant prevalence of polygenic dyslipidemia.

Molecular landscape

The *LDLR* gene was the most frequently affected gene in our population, encompassing 94 single nucleotide variants (SNVs) and 14 large deletions. Analysis of this gene revealed exons 1 and 4 as the regions with the highest mutation frequency, with a predominance of SNVs[15]. In exon 1, Class I truncating mutations (such as c.-135C>G and p.Trp4*) were observed, which resulted in the complete absence of any detectable LDLR protein. Conversely, exon 4—the longest exon in the gene—exhibits missense mutations (p.Asp168Asn and p.Glu228Lys) that affect the synthesis, maturation, and function of the LDL receptor, leading to the phenotypic variability characteristic of familial dyslipidemia (FD)[16].

This molecular heterogeneity is directly reflected in Table 1, which demonstrates a statistically significant difference in LDL-C levels ($p = 0.03$) among the different mutation-type groups. These findings confirm that these mutations have a demonstrable impact on low-density lipoprotein (LDL) transport, resulting in higher values for patients harboring truncating mutations than for those with missense variants[17]. Furthermore, the trend observed for TC ($p = 0.07$)—although it did not reach the strict threshold for statistical significance ($p < 0.05$)—suggests that the studied genetic mutations exert a specific effect on LDL metabolism and clearance rather than broadly altering the overall lipid profile. This finding is consistent with the fact that total cholesterol is highly influenced by external factors such as diet, age, and physical activity.

Geographic distribution

Geographically, the Andean region had the highest proportion of positive findings, likely due to superior healthcare infrastructure and better access to specialized services than underserved regions such as Chocó, Vaupés, and Vichada[18]. Genomic analysis revealed distinct regional clustering; for example, 9 out of 11 patients harboring the 2.2 kb deletion in *LDLR* at the 19p13.2 locus originated from Valle del Cauca, and three individuals had a history of consanguinity. Although this suggests a potential founder effect or familial aggregation, further population-based studies are needed to confirm this regional prevalence.

The most prevalent pathogenic variant was *LDLR* c.11G>A (p.Trp4*), historically known as FH-Columbia-1[19], a nomenclature likely stemming from a misnomer or phonetic transcription error attempting to reference its Colombian origin. Although it has been described in Spain and Mexico[20], its overrepresentation in our cohort—particularly in the Caribbean region—highlights its fundamental contribution to the molecular spectrum of familial hypercholesterolemia in Colombia[21]. Similarly, the *LDLR* c.-135C>G (FH-Columbia-2) variant reached its highest reported frequency in our study, despite having been documented in Portugal[22], Spain[23], the United Arab Emirates (UAE)[24], and Argentina[25].

The *LDLR* c.682G>A (p.Glu228Lys) variant showed regional aggregation in Santander, despite being previously described in Latin America[26], Asia[27], and Europe[28]. Furthermore, the high frequency of the *APOB* c.10580G>A (p.Arg3527Gln) variant, originally described in Europe, provides insight into historical migration patterns. Additionally, we report the first case of the 'Lebanese allele' in a Colombian patient of Arab descent, which is consistent with migration patterns to the Atlantic coast[29].

Among the most frequent CNVs and SNVs detected in the *LDLR* gene, only the *LDLR* c.-135C>G variant was shared with other Ibero-American populations, while the rest of the genetic profile proved to be particularly characteristic of our cohort[21].

Our findings indicate that expanding the size of the genetic panel does not proportionally increase the positivity rate. Regarding zygosity, 0.58% of our cohort presented homozygous familial dyslipidemia (HoFD), characterized by severe mixed dyslipidemia since childhood and a mean total cholesterol of 328 mg/dL despite pharmacological intervention. Furthermore, symptomatic carriers were also observed, presenting exclusively with heterozygous variants in the *LIPA* and *ABCG5/G8* genes, alongside altered LDL-C and TC levels. Phenocopies of familial hypercholesterolemia (FH) are frequently exhibited by these patients. Despite the absence of impact on the LDLR pathway, the clinical manifestations of this group closely resemble those of FH and, as such, should be considered in patients with severe hypercholesterolemia.[30].

As shown in Figure 5, there is a high frequency of variants of uncertain significance (VUS) across different regions of Colombia, for which there is currently no documented clinical evidence. Systematic data collection remains essential for their future reclassification, and longitudinal follow-up based on future research will be crucial to definitively classify these findings as benign or pathogenic.

Variant co-occurrence

The clinical utility of comprehensive genomic sequencing in our cohort is underscored by the identification of complex genotypic profiles, such as double heterozygosity. Specifically, we identified a patient harboring concurrent variants in a gene involved in the cholesterol pathway (*LDLR*) and a gene associated with triglyceride metabolism (*APOA5*). The pathogenic variant *LDLR* c.2068del (p.His690Thrfs*19) is a well-documented cause of familial hypercholesterolemia (FH), notably reported in Czech populations[31]. Conversely*, the APOA5* c.124del (p.Glu42Serfs*15) variant was recently identified in a Brazilian patient with hypertriglyceridemia. Heterozygous variants in *APOA5* typically increase susceptibility to hypertriglyceridemia rather than being a direct cause[32], and pediatric carriers often remain asymptomatic until adulthood[33]. This well-established incomplete penetrance likely explains the absence of elevated triglycerides in our pediatric patient. Furthermore, the normal triglyceride levels observed in the carrier parent could be attributed to long-term lipid-lowering therapy.

Finally, we identified a novel variant: *LDLR* c.1955T>G (p.Met652Arg). This variant is absent or has an extremely low allele frequency in population reference databases such as gnomAD, additionally, multiple *in silico* predictive tools classify it as deleterious, with a REVEL score ≥0.75 and patient's phenotype or family history is highly specific for a disease with a single genetic etiology. According to ACMG criteria, this variant is classified as Variant of Uncertain Significance (VUS); it has not been previously reported in public databases or the literature, although this variant fulfills multiple ACMG/ClinGen criteria for pathogenicity, the current lack of functional studies demonstrating its deleterious effect precludes the application of strong evidence required for its reclassification as pathogenic.

Genomic contributions and clinical impact

This study substantially advances the genomic characterization of familial dyslipidemias in Colombia, addressing the critical underrepresentation of Latin American populations in global genomic research. Our findings reveal marked genetic heterogeneity without a single dominant founder allele; instead, the presence of variants previously described in European, Asian, and Middle Eastern populations reflects the complex migratory history and ancestral admixture of the Colombian population.

The absence of monogenic variants in a substantial proportion of patients with high clinical suspicion underscores the multifactorial etiology of dyslipidemias, where lifestyle, metabolic conditions, and pharmacological agents converge. Therefore, exercising greater rigor when requesting genetic testing, prioritizing patients for whom the results will directly impact clinical outcomes or pharmacological management, is essential.

While this study has important strengths, several limitations must be acknowledged. First, geographic distribution reflects patient referral patterns and does not necessarily represent the true national prevalence of inherited dyslipidemias. Compounding this is an inherent selection bias, as the cohort consists of individuals with established access to the healthcare system via an EPS. Second, because our exome analysis focused strictly on monogenic causes, we did not evaluate polygenic risk scores (PRS), which would likely explain a substantial portion of the negative results. Third, retrospective clinical data were incomplete for a small subset of the sample or patients cohort; specifically, baseline lipid profiles were unavailable for 17 of the 128 patients with positive genetic findings. Furthermore, we were unable to perform family segregation analysis or cascade testing for all patients, limiting our ability to confirm the genetic phase in certain compound heterozygous cases. Finally, the current lack of functional studies for novel variants and variants of uncertain significance (VUS) precludes definitive pathogenic reclassification at this time.

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Declaration of competing interest

The authors declare that they have no conflicts of interest with the contents of this article.

Availability of data and materials

The de-identified and aggregated datasets supporting the conclusions of this article are included within the article and its supplementary files, ensuring that no individual participant information is disclosed. Due to institutional policy restrictions, the full raw dataset cannot be deposited in a public repository.

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REFERENCES

1. Ruiz, Á. J., Vargas-Uricoechea, H., Urina-Triana, M., Román-González, A., Isaza, D., Etayo, E., Quintero, A., Molina, D. I., Toro, J. M., Parra, G., Merchán, A., Cadena, A., Lozano, H. Y., Cárdenas, J. M., Quintero, Á. M., Botero, R., Jaramillo, M., Arteaga, J. M., Vesga-Angarita, B., Betancur-Valencia, M. (2020). Dyslipidaemias and their treatment in high complexity centres in Colombia. Clínica E Investigación En Arteriosclerosis, 32(3), 87-134. https://doi.org/10.1016/j.arteri.2019.11.005
2. Vaezi, Z., & Amini, A. (2022, 26 septiembre). Familial hypercholesterolemia. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK556009/
3. Lenin, C., Lim, P. X. H., Nastar, A., Subramaniam, T., Pek, S., Daccord, M., Evans, E., Print, E., Chan, F. H. F., & Griva, K. (2025b). Facilitators and Barriers to Uptake of Genetic and Cascade Testing in Familial Hypercholesterolemia: a Systematic Review. International Journal Of Behavioral Medicine, 33(1), 69-82. https://doi.org/10.1007/s12529-025-10357-y
4. Zimmerman, J., Duprez, D., Veach, P. M., & Zierhut, H. A. (2018). Barriers to the identification of familial hypercholesterolemia among primary care providers. Journal Of Community Genetics, 10(2), 229-236. https://doi.org/10.1007/s12687-018-0383-3
5. World Health Organization. (2021). WHO guidelines on physical activity and sedentary behavior - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK581973/
6. Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., Grody, W. W., Hegde, M., Lyon, E., Spector, E., Voelkerding, K., & Rehm, H. L. (2015). Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics In Medicine, 17(5), 405-424. https://doi.org/10.1038/gim.2015.30
7. Lehrman, M. A., Schneider, W. J., Brown, M. S., Davis, C. G., Elhammer, A., Russell, D. W., & Goldstein, J. L. (1987). The Lebanese allele at the low density lipoprotein receptor locus. Nonsense mutation produces truncated receptor that is retained in endoplasmic reticulum. The Journal of Biological Chemistry, 262(1), 401–410. https://doi.org/10.1016/s0021-9258(19)75941-9
8. Reeskamp, L. F., Tromp, T. R., Defesche, J. C., Grefhorst, A., Stroes, E. S., Hovingh, G. K., & Zuurbier, L. (2020). Next-generation sequencing to confirm clinical familial hypercholesterolemia. European journal of preventive cardiology, 2047487320942996. Advance online publication. https://doi.org/10.1177/2047487320942996
9. Ahmad, Z. S., Andersen, R. L., Andersen, L. H., O'Brien, E. C., Kindt, I., Shrader, P., Vasandani, C., Newman, C. B., deGoma, E. M., Baum, S. J., Hemphill, L. C., Hudgins, L. C., Ahmed, C. D., Kullo, I. J., Gidding, S. S., Duffy, D., Neal, W., Wilemon, K., Roe, M. T., Rader, D. J., Knowles, J. W. (2016). US physician practices for diagnosing familial hypercholesterolemia: data from the CASCADE-FH registry. Journal of clinical lipidology, 10(5), 1223–1229. https://doi.org/10.1016/j.jacl.2016.07.011
10. Rodgers, J. L., Jones, J., Bolleddu, S. I., Vanthenapalli, S., Rodgers, L. E., Shah, K., Karia, K., & Panguluri, S. K. (2019). Cardiovascular Risks Associated with Gender and Aging. Journal of cardiovascular development and disease, 6(2), 19. https://doi.org/10.3390/jcdd6020019

11. Brown, E. E., Sturm, A. C., Cuchel, M., Braun, L. T., Duell, P. B., Underberg, J. A., Jacobson, T. A., & Hegele, R. A. (2020). Genetic testing in dyslipidemia: A scientific statement from the National Lipid Association. Journal of clinical lipidology, 14(4), 398–413. https://doi.org/10.1016/j.jacl.2020.04.011
12. Bellows, B. K., Khera, A. V., Zhang, Y., Ruiz-Negrón, N., Stoddard, H. M., Wong, J. B., Kazi, D. S., de Ferranti, S. D., & Moran, A. E. (2022). Estimated Yield of Screening for Heterozygous Familial Hypercholesterolemia With and Without Genetic Testing in US Adults. Journal of the American Heart Association, 11(11), e025192. https://doi.org/10.1161/JAHA.121.025192
13. Nagahara, K., Tada, H., & Dobashi, K. (2026). Genetic Testing for Children with Familial Hypercholesterolemia. Journal of atherosclerosis and thrombosis, 33(3), 237–248. https://doi.org/10.5551/jat.RV22046
14. Ministry of Health and Social Protection. (n.d.). *Resumen política obesidad infantil: Una amenaza silenciosa* [Summary of childhood obesity policy: A silent threat]. Repositorio Institucional Digital (RID). https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/DE/PES/resumen-politica-obesidad-infantil-amenaza-silenciosa.pdf
15. Barbosa, T. K. A., Hirata, R. D. C., Ferreira, G. M., Borges, J. B., De Oliveira, V. F., Gorjão, R., Da Silva Marçal, E. R., Gonçalves, R. M., Faludi, A. A., De Freitas, R. C. C., Dagli-Hernandez, C., Bortolin, R. H., Bastos, G. M., Pithon-Curi, T. C., Nader, H. B., & Hirata, M. H. (2022). LDLR missense variants disturb structural conformation and LDLR activity in T-lymphocytes of Familial hypercholesterolemia patients. Gene, 853, 147084. https://doi.org/10.1016/j.gene.2022.147084
16. Hu, Y., Wu, M., Yu, H., Wu, Q., Chen, Y., Zhang, J., Ruan, D., Zhang, Y., Zou, J., Zhang, L., Lin, X., Fang, Z., Liao, L., Lin, F., Li, H., & Luo, J. (2024). Analysis of low-density lipoprotein receptor gene mutations in a family with familial hypercholesterolemia. PLoS ONE, 19(10), e0310547. https://doi.org/10.1371/journal.pone.0310547
17. Tada, H., Kojima, N., Yamagami, K., Nomura, A., Nohara, A., Usui, S., Sakata, K., Fujino, N., Takamura, M., & Kawashiri, M. A. (2022). Effects of Different Types of Pathogenic Variants on Phenotypes of Familial Hypercholesterolemia. Frontiers in genetics, 13, 872056. https://doi.org/10.3389/fgene.2022.872056).
18. Galvis-Aponte, L. A., & Rico, J. N. (2023). Desigualdades regionales en la salud en Colombia [Regional inequalities in health in Colombia] (Documentos de Trabajo sobre Economía Regional y Urbana No. 316). Banco de la República. https://doi.org/10.32468/dtseru.316
19. Hobbs HH, Brown MS, Goldstein JL. Molecular genetics of the LDL receptor gene in familial hypercholesterolemia. Hum Mutat. 1992;1(6):445-66. doi: 10.1002/humu.1380010602. PMID: 1301956.
20. Robles-Osorio, L., Huerta-Zepeda, A., Ordóñez, M. L., Canizales-Quinteros, S., Díaz-Villaseñor, A., Gutiérrez-Aguilar, R., Riba, L., Huertas-Vázquez, A., Rodríguez-Torres, M., Gómez-Díaz, R. A., Salinas, S., Ongay-Larios, L., Codiz-Huerta, G., Mora-Cabrera, M., Mehta, R., Gómez Pérez, F. J., Rull, J. A., Rabès, J. P., Tusié-Luna, M. T., Durán-Vargas, S., … Aguilar-Salinas, C. A. (2006). Genetic heterogeneity of autosomal dominant hypercholesterolemia in Mexico. Archives of medical research, 37(1), 102–108. https://doi.org/10.1016/j.arcmed.2005.04.018
21. Ruiz, Álvaro J., Patiño, Luisa Fernanda, Amaya, Kelly, Gómez, Juan Esteban, Ordóñez, Felipe, Paternina, Samuel, Mercado, Misael, Pachajoa, Harry, Campo, Rafael, Giraldo, Gustavo, Jimenez, Ravagly, Zuluaga, Nohora, Monroy, Jeniffer, Gil-Forero, Julián, Matallana, Audrey, Rivera, Carolina, Coll, Mauricio, Peña, William, Manjarrez, Octavio, Toro, Juan Martín, Barrera, Álvaro, Hoyos, Diego, & García, Harold. (2020). Hipercolesterolemia familiar: serie de 36 casos con fenotipo de hipercolesterolemia familiar homocigótica. Revista Colombiana de Cardiología, 27(6), 501-510. Epub July 14, 2021.https://doi.org/10.1016/j.rccar.2019.10.006
22. Santos, R. D., Bourbon, M., Alonso, R., Cuevas, A., Vasques-Cardenas, N. A., Pereira, A. C., Merchan, A., Alves, A. C., Medeiros, A. M., Jannes, C. E., Krieger, J. E., Schreier, L., Perez de Isla, L., Magaña-Torres, M. T., Stoll, M., Mata, N., Dell Oca, N., Corral, P., Asenjo, S., Bañares,

V. G., Ibero-American Familial Hypercholesterolemia Network (2017). Clinical and molecular aspects of familial hypercholesterolemia in Ibero-American countries. Journal of clinical lipidology, 11(1), 160–166. https://doi.org/10.1016/j.jacl.2016.11.004

23. Civeira, F., Jarauta, E., Cenarro, A., García-Otín, A. L., Tejedor, D., Zambón, D., Mallen, M., Ros, E., & Pocoví, M. (2008). Frequency of low-density lipoprotein receptor gene mutations in patients with a clinical diagnosis of familial combined hyperlipidemia in a clinical setting. Journal of the American College of Cardiology, 52(19), 1546–1553. https://doi.org/10.1016/j.jacc.2008.06.050
24. Rimbert, A., Daggag, H., Lansberg, P., Buckley, A., Viel, M., Kanninga, R., Johansson, L., Dullaart, R. P. F., Sinke, R., Al Tikriti, A., Kuivenhoven, J. A., & Barakat, M. T. (2022). Low Detection Rates of Genetic FH in Cohort of Patients With Severe Hypercholesterolemia in the United Arabic Emirates. Frontiers in genetics, 12, 809256. https://doi.org/10.3389/fgene.2021.809256
25. Bañares, V. G., Corral, P., Medeiros, A. M., Araujo, M. B., Lozada, A., Bustamante, J., Cerretini, R., López, G., Bourbon, M., & Schreier, L. E. (2017). Preliminary spectrum of genetic variants in familial hypercholesterolemia in Argentina. Journal of clinical lipidology, 11(2), 524–531. https://doi.org/10.1016/j.jacl.2017.02.007
26. Vaca, G., Vàzquez, A., Magaña, M. T., Ramìrez, M. L., Dàvalos, I. P., Martìnez, E., Marìn, B., & Carrillo, G. (2011). Mutational analysis of the LDL receptor and APOB genes in Mexican individuals with autosomal dominant hypercholesterolemia. Atherosclerosis, 218(2), 391–396. https://doi.org/10.1016/j.atherosclerosis.2011.06.006
27. Kim, H. N., Kweon, S. S., & Shin, M. H. (2018). Detection of Familial Hypercholesterolemia Using Next Generation Sequencing in Two Population-Based Cohorts. Chonnam medical journal, 54(1), 31–35. https://doi.org/10.4068/cmj.2018.54.1.31
28. Kusters, D. M., Huijgen, R., Defesche, J. C., Vissers, M. N., Kindt, I., Hutten, B. A., & Kastelein, J. J. (2011). Founder mutations in the Netherlands: geographical distribution of the most prevalent mutations in the low-density lipoprotein receptor and apolipoprotein B genes. Netherlands heart journal : monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation, 19(4), 175–182. https://doi.org/10.1007/s12471-011-0076-6
29. De Moya-Guerra L. C. y Vidal Ortega A. (2021). Migración árabe a Barranquilla: el caso de Elías Muvdi. Anaquel de Estudios Árabes, 32, 141-154. https://doi.org/10.5209/anqe.69395
30. Ahmad, Z., Agarwala, A., Cuchel, M., Duell, P. B., Hegele, R. A., Hudgins, L., Jamison, A., Kalra, D., Khera, A., Knowles, J. W., Kullo, I. J., Morales, A., Rothstein, M. A., Saseen, J. J., Soffer, D. E., Warden, B. A., Weintraub, W. S., Williams, L., & Goldberg, A. C. (2026b). Update on familial hypercholesterolemia: An expert clinical consensus from the National Lipid Association. Journal Of Clinical Lipidology, 20(4), 708-737. https://doi.org/10.1016/j.jacl.2026.01.011

31. Tichý, L., Freiberger, T., Zapletalová, P., Soška, V., Ravčuková, B., & Fajkusová, L. (2012). The molecular basis of familial hypercholesterolemia in the Czech Republic: spectrum of LDLR mutations and genotype-phenotype correlations. *Atherosclerosis*, *223*(2), 401–408. https://doi.org/10.1016/j.atherosclerosis.2012.05.014
32. Mendes, C., Loureiro, T., Villela, D., Bittencourt, M. I., Sobreira, J., Bermeo, D., Gomes, M., Alencar, D., de Castro, L. S. S., Fock, R. A., Tinoco, M. L., Galvão, H., Scapulatempo-Neto, C., Schiavetti, K., Senerchia, A. A., & Gurgel, M. H. C. (2024). Germline variant analysis from a cohort of patients with severe hypertriglyceridemia in Brazil. Molecular genetics and metabolism reports, 40, 101100. https://doi.org/10.1016/j.ymgmr.2024.101100
33. Moreno Tirado, A., Rodríguez Ortega, P., & Calle Isorna, J. M. (2024). Incidental diagnosis of familial apolipoprotein A5 deficiency. Diagnóstico incidental de deficiencia de apolipoproteínaA5 familiar. *Medicina clinica*, *163*(3), 156–157. https://doi.org/10.1016/j.medcli.2024.01.043

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